REMARKS

Claims 27, 29-33, 44, and 46 are currently pending in this application. Claims 44 and 45 are objected to for being in improper form. Claims 27, 29-33, 44, and 46 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description and for lack of enablement. Claims 27, 29-33, 44, and 46 are rejected for obviousness-type double patenting over claims 1-11 of U.S. Patent No. 6,372,432. The Examiner objects to the title of the application for being insufficiently descriptive. The Examiner also objects to the specification for improper incorporation of patent and non-patent documents by reference. By this reply, Applicants cancel claim 46, amend claim 27, add new claims 47-49, and address each of the objections and rejections. Applicants reserve the right to pursue cancelled subject matter in a divisional application.

Support for the Amendments

Support for the amendment to claim 27 and for new claims 47-49 is found in present claim 27 and in the specification at, e.g., page 2, lines 27-30, and page 3, lines 9-11. Support for the amendment to the specification is addressed below. No new matter is added by the amendment.

Objection to the Title

The Examiner objects to the title of the application because it is insufficiently descriptive of the invention. Applicants have amended to the title to more clearly describe the invention recited in present claims 27, 29-33, 44, and 47-49. This objection can now be withdrawn.

Objection to the Specification

The Examiner objects to the specification, stating:

> The specification is objected to as documents have been improperly incorporated by reference. It is noted with particularity that the instant disclosure makes reference to various foreign patent document[s], both published and unpublished, as well as non-patent publications which are in turn being relied upon for disclosing how the claimed invention is to be made and used. Office Action, p. 2.

The Examiner further states that the language used in the specification "fails to specify what specific information applicant seeks to incorporate by reference and just where the specific information is to be found in each of the cited documents" (Office Action, p. 3). In response, Applicants have amended the specification to include "incorporation by reference" statements indicating that the material described is intended to be incorporated into the specification. As is stated in the M.P.E.P. § 608.01(p)(I)(A)(2):

> A noncompliant incorporation by reference statement may be corrected by an amendment. 37 CFR 1.57(f). However, the amendment must not include new matter...37 CFR 1.57(g)(1) authorizes the correction of noncompliant incorporation by reference statements that do not use the root of the words "incorporate" and "reference" in the incorporation by reference statement. This correction cannot be made when the material was merely referred to and there was no clear specific intent to incorporate it by reference. 37 CFR 1.57(g)(2) states that a citation of a document can be corrected where the document is sufficiently described to uniquely identify the document. Correction of a citation for a document that cannot be identified as the incorporated document may be new matter and is not authorized by 37 CFR 1.57(g)(2). An example would be where applicant intended to incorporate a particular journal article but supplied the citation information for a completely unrelated book by a different author, and there is no other information to identify the correct journal article. Since it cannot be determined from the citation originally supplied what article was intended to be incorporated, it would be improper (e.g., new matter) to replace the original incorporation by reference with the intended incorporation by reference. A citation of a patent application by attorney docket number, inventor name, filing date and title of invention may sufficiently describe the document, but even then correction should be made to specify the application number.

Applicants' amendment to the specification is compliant with the incorporation by reference requirements of 37 C.F.R. § 1.57. Namely, the present amendments satisfy the requirements of 37 C.F.R. § 1.57(g)(1) because the present specification provides a clear intent by Applicants that the subject matter described was sought to be incorporated by reference (e.g., with respect to the Miller and Riblet reference, page 18, lines 17-24, states "The hybridization is advantageously [sic] carried out in a phenol emulsion maintained by thermocycling (temperature increase from approximately 37°C to approximately 60/65°C) and not by agitation, according to the method described by Miller and Riblet (NAR 23 (1995) 2339)," and page 28, lines 12-14, which references International Application No. PCT/FR99/00547, states "These hybridizations are carried out according to methods familiar to those skilled in the art (in particular, consult the hybridization conditions set forth in application No. PCT/FR99/00547)"). Thus, by reference to the various publicly available publications and foreign applications, Applicants have clearly indicated their intent that the described subject is to be made a part of Applicants' specification. In any event, all that is required by law for an incorporation by reference of subject matter into a specification, in the case of publicly available documents, is for Applicants to provide a citation to the document and to describe the subject matter sought to be incorporated; both of which Applicants have clearly done (*see In re Georg Stauber*, 45 F.2d 661 (C.C.P.A. 1930)).

The present amendments to the specification also satisfy the requirement of 37 C.F.R. § 1.57(g)(2) because the documents sought to be incorporated by reference are sufficiently described to uniquely identify the documents and to describe the subject with particularity. As is made clear by the M.P.E.P. § 608.01(p)(I)(A)(2) with respect to citations to journal articles,

Applicants need only provide identifying information about the article, such as the name of the author(s), the journal name, the volume number, the page number(s), and the publication date; providing accurate information about the citation is sufficient to satisfy 37 C.F.R. § 1.57(g)(2). Furthermore, by law, satisfaction of the "particularity" standard occurs by "identifying the subject matter which is incorporated and where it is to be found" (i.e., simply providing the citation itself, not the location in the citation where the information can be found; *see In re Seversky*, 474 F.2d 671 (Fed. Cir. 1973)). Thus, Applicants have satisfied this requirement as well.

Finally, Applicants note that the material sought to be incorporated is nonessential material (37 C.F.R. § 1.57(d)). Furthermore, as required by 37 C.F.R. § 1.57(f), Applicants state that the material being inserted is the material previously incorporated by reference and the amendment to the specification contains no new matter. Applicants respectfully submit that this objection can now be withdrawn.

Obviousness-Type Double-Patenting Rejections

Claims 27, 29-33, 44, and 46 are rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,372,432. Applicants will submit a terminal disclaimer, if necessary, to overcome this rejection once otherwise allowable subject matter has been determined.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 27, 29-33, 44, and 46 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner states that "[t]he claim(s) contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (Office Action, p. 6). The Examiner continues by stating:

> A review of the specification fails to find where applicant had contemplated, much less fully described, pathologies other than cancer, stenosis and neurodegenerative disorders as being applicable to a general method of detecting pathologies in organisms, much less to detecting such pathologies in humans and then using only lymphocytes, macrophages, monocytes or dendritic cells, to which claim 27 is now limited. (Office Action, p. 8.)

Applicants respectfully disagree with the Examiner's conclusion, but have amended claim 27 to more clearly describe the claimed invention. In particular, claim 27 now specifies that the method is for the remote detection of a pathology in a subject (i.e., by using test samples that are distinct from the diseased tissues). This feature is particularly advantageous because it allows a skilled artisan, using the methods disclosed in the present specification, to test for the presence of a given pathological condition using blood samples, which are much easier to manipulate and are less invasive for the patient than other art known procedures. In addition, claim 27 now specifies that the pathological condition is associated with a deregulation in a cell signaling pathway, more specifically with an excessive cell proliferation, as is recited in new claim 47, which depends from claim 27, and in new independent claim 48. Thus, claim 27, as presently amended, reads

only on pathologies that involve a deregulation in a cell signaling pathway, which can be identified by alternative splicing events.

It is submitted that the specification provides a full and detailed written description of how to implement the methods of present claims 27, 29-33, 44, and 47-49, as presently amended, in their whole breadth. The specification teaches new methods for detecting pathological conditions in a subject, based on gene splicing modifications that occur in blood cells in response to the pathological condition. This concept is illustrated in the specification by several examples, including cancers and neurodegenerative diseases, but is not limited to these examples alone. For the reasons discussed below, the present specification satisfies the written description requirement of 35 U.S.C. § 112, first paragraph, and supports the full scope of present claims 27, 29-33, 44, and 47-49.

"To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention" (M.P.E.P. § 2163). Possession of a claimed invention can be demonstrated by describing the invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention (*Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997)). The written description standard **does not require** a detailed description of those features of an invention that were well known to or understood by the skilled artisan at the time of filing, but rather, "[t]he description need only describe in detail that which is new or not conventional" (*Hybritech v. Monoclonal Antibodies, supra*; emphasis added). Therefore, to satisfy the written description requirement, Applicants need only describe in detail those features

that were not new or were unconventional in the art at the time of filing. Applicants have plainly satisfied this standard.

Each of the methods of present independent claims 27, 47, and 49, and claims dependent therefrom, require three steps: i) obtaining a sample of blood cells (i.e., lymphocytes, macrophages, monocytes, or dendritic cells) from a human test subject; ii) preparing nucleic acid molecules from the sample; and iii) obtaining a hybridization profile by hybridizing all or part of the nucleic acid molecules prepared in step ii) with at least one nucleic acid library, in which the nucleic acid library contains a plurality of nucleic acid molecules specific for differentially spliced ribonucleic acid molecules (RNAs) expressed in blood cells from human subjects having the pathological condition sought to be detected in the test subject. Hybridization of nucleic acid molecules from the test subject's sample with nucleic acid molecules of the library indicates the presence of the pathological condition in the test subject. Applicants have described the claimed methods with all of its limitations and have satisfied the written description requirement of 35 U.S.C. § 112 (*Lockwood v. American Airlines, Inc.*, *supra*).

For example, isolation of a blood sample can be performed as described on page 6, line 26 to page 7, line 5. Extraction of nucleic acids can be performed, for example, as described on page 7, lines 5-14, or page 10, lines 16 through page 11, line 9. Preparation of the particular nucleic acid libraries and hybridization of the nucleic acids of the library with a test sample containing nucleic acids can be performed following the guidance provided, for example, on page 12, line 15, to page 21, line 28. Furthermore, the specification teaches that these methods can be used to detect pathological conditions, e.g., various cancers or neurodegenerative diseases, such as breast cancer (see, e.g., page 1, lines 18-20, page 29, line 27), liver cancer (see, e.g., page

26, line 8, through page 27, line 12), breast, lung, prostate, liver, and bone cancers (see, for example, page 4, lines 25-30), Alzheimer's disease (see, e.g., page 1, lines 21-22), Huntington's disease, Parkinson's disease (see, e.g., page 14, line 31, through page 15, line 1), amytrophic lateral sclerosis (ALS), and epilepsy (see, e.g., page 15, lines 16-17). Thus, each of the limitations of present claims 27, 29-33, 44, and 47-49 are described in considerable detail in Applicants' specification.

The Examiner, though, states that "the specification has not identified any specific form of cancer that can be identified...[using lymphocytes, macrophages, monocytes, or dendritic cells], much less teach what an informative hybridization profile would look like" and no

> part of the disclosure has been found to set forth a full, clear, and concise description of the invention such that one would be able to identify any human cancer, much less cancers such as solid tumors of the liver, lungs, head and neck, melanoma, liver, bladder, breast, etc., or for that matter, any other human pathology. (Office Action, p. 8.)

Applicants respectfully point out that the invention of present claims 27, 29-33, 44, and 47-49 is **not** the identification of genetic markers correlating to a given, predefined pathological condition; such markers were already well defined in the art prior to Applicants' invention date or were obtainable using methods known in the art at the time the application was filed (as was thoroughly discussed on page 22 of the Reply to Office Action filed on August 4, 2004), and thus Applicants need not disclose this information to satisfy the written description requirement (*Hybritech v. Monoclonal Antibodies*, *supra*); a fact which the Examiner has acknowledged (see page 12 of the present Office Action). Rather, Applicants' invention, which is recited in present claims 27, 29-33, 44, and 47-49, is the discovery that various pathological conditions, which involve a deregulation in a cell signaling pathway, such as, e.g., cancers, neurological diseases,

and stenosis, can be detected remotely using nucleic acid molecules isolated from lymphocytes, macrophages, monocytes, or dendritic cells of the test subject (e.g., a patient). The isolated nucleic acid molecules obtained from these cells are hybridized to a nucleic acid library that contains nucleic acid molecules specific for differentially spliced ribonucleic acid molecules (RNAs) expressed in blood cells from human subjects having the given, predefined pathological condition; the differentially spliced RNAs of the library are indicative of the given, predefined pathological condition. The hybridization step yields a hybridization profile in which the result is simply binary: hybridization of the test subject's nucleic acid sample with the nucleic acids of the library indicates the presence of the pathological condition in the test subject, whereas the absence of hybridization between the test subject's nucleic acid sample and the nucleic acids of the library indicates absence of the pathological condition in the test subject. Due to the simplicity of the method and its result, Applicants submit that it is unnecessary to describe such a hybridization profile in order to satisfy the written description requirements of 35 U.S.C. § 112, first paragraph, nor would one skilled in the art doubt Applicants' possession of the invention simply because a representative hybridization profile is not disclosed in Applicants' specification. For the purposes of written description, all that is required is that Applicants' specification describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (M.P.E.P. § 2163; *Regents of the University of California v. Eli Lilly & Co., supra*). This Applicants have clearly done.

It is thus respectfully submitted that the specification provides a complete written disclosure of the invention recited in present claims 27, 29-33, 44, and 47-49, such that one

skilled in the art would recognize that Applicants were in possession of the invention. Accordingly, the specification fulfills the written description requirement of 35 U.S.C. § 112, first paragraph, and withdrawal of the rejection of claims 27, 29-33, 44, and 46 is respectfully requested.

Enablement

Claims 27, 29-33, 44, and 46 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states that "[t]he claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention" (Office Action, p. 9). Without acquiescing to the rejection, and solely in order to promote the issuance of Applicants' patent, Applicants have amended independent claim 27 to specify that the method is for the remote detection of a pathological condition associated with a deregulation in a cell signaling pathway in a subject. Applicants have also added new claim 47, which recites that the pathological condition is characterized by excessive cell proliferation. In addition, Applicants have added new independent claims 48 and 49, which are directed to methods for detecting a pathological condition associated with excessive cell proliferation and stenosis, respectively. For the reasons discussed below, the methods of present claims 27, 29-33, 44, and 47-49 are enabled to their full scope.

35 U.S.C. § 112, first paragraph, requires that the specification describe how to make and use the invention. The Court has construed this requirement to mean that both the making and the using of the invention disclosed in the specification must not involve "undue

experimentation" (see, e.g., *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993)). As is discussed above, present independent claims 27, 48, and 49 recite three method steps. The first method step, obtaining a sample of blood cells (i.e., lymphocytes, macrophages, monocytes, or dendritic cells) from a human test subject is disclosed on page 6, line 26 to page 7, line 5. The second method step, preparing nucleic acid molecules from the sample, is described on page 7, lines 5-14, or page 10, lines 16 through page 11, line 9. The third method step, obtaining a hybridization profile by hybridizing all or part of the nucleic acid molecules prepared in the second method step with at least one nucleic acid library, is described on page 12, line 15, to page 21, line 28. As is discussed above, the third method step only requires a determination of whether any of the differentially spliced nucleic acids of the library, which are characteristic of, and indicative of, the pathological condition, are present in the test sample. Thus, the "hybridization profile" is merely a binary determination – if the nucleic acids of the test sample hybridize to the nucleic acids of the library, the test subject that provided the test sample is likely to have the pathological condition, and if no nucleic acids of the test sample bind to the nucleic acids of the library, the test subject is unlikely to have the pathological condition. Therefore, because all of these method steps are disclosed in considerable, enabling detail in Applicants' specification, and because their performance would not require undue experimentation, present claims 27, 39-33, 44, and 47-49 are fully enabled.

The Examiner has provided no indication that the first and second method steps are not described in enabling detail, but with regard to the third method step, the Examiner states:

> A review of the specification fails to find where any hybridization profile has been determined for any known human pathological condition. While one is note [sic] required to teach each and every possible embodiment encompassed by the claims, the specification has not been found to teach a reproducible method whereby any specific human pathological condition

> could be identified. In short, applicant has not provided the essential starting materials and reaction conditions needed to practice even a part of the claims' scope. (Office Action, p. 10.)

Because the specification has provided all of the essential starting materials and reaction conditions needed to practice the invention of present claims 27, 39-33, 44, and 47-49, Applicants respectfully disagree with the Examiner's conclusion.

As is discussed above, the differentially spliced nucleic acid molecules of the library are expressed as a result of the pathological condition, and thus, the expression of these nucleic acid molecules in a patient can be used to identify the patients as having the pathological condition. Applicants have pointed out, and the Examiner has agreed, that the nucleic acid sequences of the probes of the library are within the art and need not be provided by Applicants (see Office Action, p. 12). Thus, the only issue raised by the Examiner is whether Applicants have enabled the use of the library to identify patients having the pathological condition.

As evidence that the invention disclosed in Applicants' specification, and as is recited in present claims 27, 39-33, 44, and 47-49, is enabled, Applicants submit a Declaration of Dr. Fabien Schweighoffer, which attests that the methods of present claims 27, 39-33, 44, and 47-49 have been successfully employed to detect the presence of bovine spongiform encephalopathy (BSE) in cattle naturally and experimentally infected with prion protein. Paragraphs 4-8 of the Declaration state that the methods of the invention have been used successfully and reliably to discriminate between healthy subjects and infected subjects having BSE, which is a pathological condition associated with a deregulation of a cell signaling pathway. The Declaration further confirms that the DATAS method, which was known in the art at the time the application was filed, was used to identify 818 differentially spliced nucleic acid markers, between animals

infected with BSE and control animals (see ¶ 6 of the Declaration). These markers, which were used as the nucleic acid library, were affixed to glass slides and used to determine whether test animals were positive or negative for the pathological condition. In particular, Dr. Schweighoffer attests that a set of 5 splicing markers (LT1-LT5) alone were sufficient to discriminate between BSE infected and non-infected animals, regardless of the stage of the disease (early or late). Paragraph 7 of the Declaration states that the splicing markers used as the library were successfully and reliably used to detect the presence of the pathological condition in infected test animals based on the hybridization of the nucleic acids from blood cells of the test animals with the nucleic acids of the library and to identify non-infected healthy animals based on the absence of any hybridization between nucleic acids from blood cells of the healthy animals with the nucleic acids of the library.

The data presented in ¶¶ 5-7 of the Declaration clearly demonstrate the remote *in vitro* detection, using only blood cells from a test subject, of the presence of a given, predefined pathological condition, BSE, according to the methods of present claims 27, 39-33, 44, and 47-49. As is clearly shown, the data demonstrate the successful preparation of a nucleic acid library characteristic of the pathological condition, using art-known techniques, and the reliable detection of that pathological condition by detecting hybridization between the nucleic acid molecules of the library and nucleic acid molecules obtained from a sample of blood cells from the test subject (i.e., the hybridization profile). Finally, Dr. Schweighoffer attests that this methodology can be used to detect any pathological condition characterized by alternative splicing events in blood cells as a result of a pathological condition, and that these results disclosed in cattle are predictive of success for detecting pathological conditions characterized by

alternative splicing events in humans (see ¶ 8 of the Declaration).

In view of Applicants remarks above and the Declaration of Dr. Fabien Schweighoffer, Applicants respectfully submit that the specification provides an enabling disclosure of the invention of present claims 27, 39-33, 44, and 47-49. The specification enables the skilled person to prepare nucleic acid libraries, to isolate nucleic acid molecules from blood samples of test subjects, to perform a hybridization step between the library and test sample, and to determine, from the results of the hybridization step, whether the test subject has a given, predefined pathological condition. It is thus submitted that the specification provides all the means and methodologies to perform the invention as claimed, so that the specification fulfills the requirements of 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection of present claims 27, 39-33, 44, and 47-49 under 35 U.S.C. § 112, first paragraph, for lack of enablement is respectfully requested.

CONCLUSION

Applicants submit that the claims are now in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for three months, to and including May 18, 2006, and a check for the fee required under 37 C.F.R. § 1.17(a).

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: May 17, 2006

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